# NEW ZEALAND DATA SHEET

## 1 PRODUCT NAME

**SEPTANEST 1:100,000 AND SEPTANEST 1:200,000** (ARTICAINE HYDROCHLORIDE, ADRENALINE (EPINEPHRINE) ACID TARTRATE) **SOLUTION FOR INJECTION**

**SEPTANEST 1:100,000**: articaine hydrochloride 4% with adrenaline (epinephrine) acid tartrate 1:100,000 [i.e. articaine hydrochloride 40 mg/mL with adrenaline (epinephrine) 10µg/mL]

**SEPTANEST 1:200,000**: articaine hydrochloride 4% with adrenaline (epinephrine) acid tartrate 1:200,000 [i.e. articaine hydrochloride 40 mg/mL with adrenaline (epinephrine) 5µg/mL]

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

| **SEPTANEST 1:100,000** | Per 1.7 mL cartridge | Per 2.2 mL cartridge |
|---|---|---|
| **Active Ingredients** | | |
| Articaine hydrochloride (INN) | 68.0 mg | 88.0 mg |
| Adrenaline (epinephrine) acid tartrate | 17.0 µg | 22.0 µg |
| **Other ingredients** | | |
| Sodium chloride | 2.72 mg | 3.52 mg |
| Sodium metabisulfite | 0.85 mg | 1.1 mg |
| Sodium hydroxide solution (to adjust pH) | | |
| Water for injection q.s ad | 1.7 mL | 2.2 mL |

Contains no antimicrobial agent.

| **SEPTANEST 1:200,000** | Per 1.7 mL cartridge | Per 2.2 mL cartridge |
|---|---|---|
| **Active Ingredients** | | |
| Articaine hydrochloride (INN) | 68.0 mg | 88.0 mg |
| Adrenaline (epinephrine) acid tartrate | 8.5 µg | 11.0 µg |
| **Other ingredients** | | |
| Sodium chloride | 2.72 mg | 3.52 mg |
| Sodium metabisulfite | 0.85 mg | 1.1 mg |
| Sodium hydroxide solution (to adjust pH) | | |
| Water for injection q.s ad | 1.7 mL | 2.2 mL |

Contains no antimicrobial agent.

Articaine hydrochloride is a local anaesthetic.

Adrenaline (epinephrine) acid tartrate is a vasoconstrictor.

# 3 PHARMACEUTICAL FORM

**SEPTANEST 1:100 000** is a Clear, not opalescent, colourless solution for injection cartridge, practically free from visible particles. It is available in a 1.7mL or 2.2mL cartridge.

**SEPTANEST 1:200 000** is a Clear, not opalescent, colourless solution for injection cartridge, practically free from visible particles. It is available in a 1.7mL or 2.2mL cartridge.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

SEPTANEST 1:100,000 is indicated for local or regional anaesthesia for both simple and complex dental procedures in adults, adolescents and children 4 years of age and older.

SEPTANEST 1:200,000 is indicated for local anaesthesia for simple dental procedures in adults, adolescents and children 4 years of age and older.

SEPTANEST 1:100,000 and SEPTANEST 1:200,000 are indicated only for dental procedures.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

One or more cartridges should be used on a single patient on one occasion only during each session of treatment. If only a portion of a cartridge is used, the remainder must be discarded.

As for any cartridge, the diaphragm should be disinfected just prior to use. It should be carefully swabbed:

- either with ethyl alcohol 70%,
- or with pure isopropyl alcohol 90% for pharmaceutical use.

The cartridges should under no circumstances be dipped into any solution whatsoever.
The solution for injection should not be mixed with any other product into the same syringe.
No opened cartridge of anaesthetic solution should be reused.

**Use in Adults**
Table 1 summarises the recommended volumes and concentrations of SEPTANEST 1:200,000 or SEPTANEST 1:100,000 for various types of anaesthetic procedures. For most common operations, one infiltration with 1.7 mL SEPTANEST 1:200,000 or SEPTANEST 1:100,000 is sufficient. In all cases, the injection must be done slowly (about 1 mL/min).
For an infiltration in the interdental septum, a quantity of 0.3 to 0.5 mL is generally sufficient. Higher volumes should rarely be required.

MAXIMUM RECOMMENDED DOSE for normal healthy adults of articaine hydrochloride administered by submucosal infiltration and/or nerve block should not exceed 7 mg/kg of body weight. This corresponds, for a subject weighing 60 kg, to six (6) standard 1.7 mL cartridges or five (5) standard 2.2 mL cartridges (doses of 7 mg/kg were not exceeded in clinical trials). Anaesthesia is obtained rapidly (1 to 6 minutes).

Table 1. Recommended Dosages

| PROCEDURE | SEPTANEST 1:200,000 or SEPTANEST 1:100,000 INJECTION | |
|---|---|---|
| | Vol (mL) | Total dose of Articaine HCl (mg) |
| Infiltration | 0.5-2.5 | 20-100 |
| Nerve Block | 0.5-3.4 | 20-136 |
| Oral Surgery | 1.0-5.1 | 40-204 |
| The above-suggested volumes serve only as a guide for normal healthy adults.<br>Other volumes may be used provided that the total maximum recommended dose is not exceeded. | | |

The duration of the anaesthesia during which an operation can be performed is about one hour (pulpal analgesia) depending on the technique used, and on the procedure.

**Use in Children**
Safety and effectiveness in paediatric patients below the age of 4 years have not been established. Dosages in paediatric patients (over 4 years) should be reduced, commensurate with age, body weight, and physical condition. Please refer to the Table 2 below. Use of SEPTANEST 1:200,000 or SEPTANEST 1:100,000 in children under 4 years of age is not recommended due to the absence of safety and efficacy data.

MAXIMUM RECOMMENDED DOSE for normal healthy children must not exceed 7mg/kg of body weight.

Table 2. Dosage Adjustments for Use in Children

| | **20kg Child** | | **40kg Child** | |
|---|---|---|---|---|
| **Maximum Dose: 0.175 mL/kg** | **3.5 mL,**<br>i.e.<br>≈ 2 cartridges of 1.7 mL<br>or<br>≈ 1.5 cartridge of 2.2 mL | | **7.0 mL,**<br>i.e.<br>≈ 4 cartridges of 1.7 mL<br>or<br>≈ 3 cartridges of 2.2 mL | |
| **Recommended dose:** | **Procedure** | | **Procedure** | |
| | Simple | Complex | Simple | Complex |
| **0.06mL/kg for simple procedure** | 1.2mL<br>i.e.<br>≈ ¾ cartridge of 1.7 mL<br>Or<br>≈ ½ cartridge of 2.2 mL | 1.4mL<br>i.e.<br>≈ ¾ cartridge of 1.7 mL<br>Or<br>≈ ½ cartridge of 2.2 mL | 2.4 mL<br>i.e.<br>≈ 1 ½ cartridge of 1.7 mL<br>Or<br>≈ 1 cartridge of 2.2 mL | 2.8 mL<br>i.e.<br>≈ 1 ½ cartridge of 1.7 mL<br>Or<br>≈ 1 cartridge of 2.2 mL |
| **0.07mL/kg for complex procedure** | | | | |

## 4.3 CONTRAINDICATIONS

Hypersensitivity to articaine (or any local anaesthetic agent of the amide type) or to adrenaline (epinephrine) or to any of the excipients.

SEPTANEST contains sodium metabisulfite, which may cause allergic reactions, including anaphylactic reactions and asthmatic episodes, in susceptible people (*see Sections 4.4 – Special warnings and precautions for use and 4.8 – Undesirable effects*).
Phaeochromocytoma

Uncontrolled hyperthyroidism
Plasma cholinesterase deficiency
Complete heart block not compensated by a pacemaker

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before using SEPTANEST, it is important:
- To make inquiries into the patient's current therapies and history;
- To maintain verbal contact with the patient.

**WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND RESUSCITATIVE DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS.**

**INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION, WHICH CAN PRODUCE CEREBRAL SYMPTOMS EVEN AT LOW DOSES.**

### Special Warnings

**SEPTANEST must be used with caution in:**
*Patients with cardiovascular disorders:*
- Uncontrolled/severe hypertension
- Severe ischemic heart disease
- Recent myocardial infarction
- Recent coronary artery bypass surgery
- Persistent/refractory tachyarrhythmia
- Atrioventricular block grade I, II and III; do not use in complete heart block (grade III) not compensated by a pacemaker
- Peripheral vascular disease
- Heart failure
- Hypotension.

For all patients with cardiovascular disorders, the lowest dose leading to efficient anaesthesia should be used. For patients with severe uncontrolled hypertension, unstable angina, recent myocardial infarction (<6 months), recent coronary artery bypass graft surgery (<3 months), or severe/refractory arrhythmias, elective dental treatment should be postponed. Stress and anxiety reduction is crucial in the management of patients with cardiovascular disorders.

*Patients with epileptic disease:*
Because of their convulsive actions, all local anaesthetics should be used very cautiously, particularly in those patients with poorly-controlled disease. Stress reduction procedures should be employed to minimize the risk of a seizure developing during treatment.

*Patients with plasma cholinesterase deficiency*
A plasma cholinesterase deficiency can be suspected when clinical signs of overdose occurs with usual dosage of anaesthesia and when a vascular injection has been excluded. In this case the subsequent use of products containing articaine should be avoided (*see Section 4.3 – Contraindications*).

*Patients with myasthenia gravis:*
The lowest dose leading to efficient anaesthesia should be used.

*Patients receiving treatment with antiplatelets / anticoagulants:*
The increased risk of severe bleeding after accidental vessel puncture and during oro-maxillo-facial surgery should be considered. INR monitoring should be increased in patients taking anticoagulants.

*Patients receiving treatment with Monoamine Oxidase Inhibitors (MAOis):*
SEPTANEST must be used with caution in patients receiving concomitant treatment with MAOi.

*Patients with porphyria:*
SEPTANEST should be used cautiously.

*Patients with diabetes:*
The use of SEPTANEST in those with uncontrolled diabetes mellitus is not advised due to the hyperglycaemic effect of adrenaline (epinephrine). SEPTANEST should be used with caution in those patients with diabetes mellitus which is well-controlled by diet or oral hypoglycaemic agents. Patients treated with insulin may be at greater risk of complications following the administration of adrenaline (epinephrine)..

*Patients with susceptibility of acute angle-closure glaucoma:*
SEPTANEST should be used cautiously due to the presence of adrenaline (epinephrine) which may precipitate acute angle closure.

*Patients with cerebrovascular insufficiency:*
Due to the presence of adrenaline (epinephrine), vasoconstriction may occur in patients with cerebrovascular insufficiency, leading to a risk of transient cerebral ischaemia.
Reduced doses should be used to minimise the risk of transient cerebral ischaemia

***SEPTANEST must be used safely and effectively under appropriate conditions:***

Adrenaline (epinephrine) impairs the flow of blood in the gums, potentially causing local tissue necrosis.

Very rare cases of prolonged or irreversible nerve injury and gustatory loss have been reported after mandibular block analgesia.

The local anaesthetic effects may be reduced and the risk of systemic adverse effects increased when **SEPTANEST** is injected into an inflamed or infected area.

Risk of biting trauma (lips, cheeks, mucosa, and tongue) exists, especially in children; the patient should be told to avoid chewing gum or eating until normal sensation is restored.

**SEPTANEST** contains sodium metabisulfite, a sulfite that may rarely cause hypersensitivity reactions and bronchospasm.

**SEPTANEST** contains less than 1 mmol sodium (23 mg) per cartridge, i.e. it is considered as essentially “sodium free“.

## Precautions for use

*Risk associated with accidental intravascular injection:*
Accidental intravascular injection may cause sudden high levels of adrenaline (epinephrine) and articaine in the systemic circulation. This may be associated with severe adverse reactions, such as convulsions, followed by central nervous and cardiorespiratory depression and coma, progressing to respiratory and circulatory arrest. Thus, to ensure that the needle does not penetrate a blood vessel during injection, aspiration should be performed before the local anaesthetic product is injected. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors or drowsiness may be early warning signs of central nervous system toxicity (*see Section 4.9 - Overdose*).

*Risk associated with intraneural injection:*
Accidental intraneural injection may lead the drug to move in retrograde manner along the nerve. In order to avoid intraneural injection and to prevent nerve injuries in connection with nerve blockades, the needle should always be slightly withdrawn if electric shock sensation is felt by the patient during injection or if the injection is particularly painful. If needle nerve injuries occur, the neurotoxic effect could be aggravated by articaine potential chemical neurotoxicity and the presence of adrenaline (epinephrine) as it may impair the perineural blood supply and prevent articaine local wash-out. The risk of nerve damage is likely to be greater if repeated injections are given into a previously anaesthetised site or if higher concentration local anaesthetic solutions are administered.
Concomitant use of other medicinal products may require thorough monitoring (*see section 4.5 - Interactions with other medicinal products and other forms of interactions*).

### Use in hepatic impairment

The lowest dose leading to efficient anaesthesia should be used.

### Use in renal impairment

The lowest dose leading to efficient anaesthesia should be used.

### Use in the elderly

In patients over 70 years old, the lowest dose leading to efficient anaesthesia should be used.

### Paediatric use

SEPTANEST should not be used in children younger than 4 years of age as safety and effectiveness have not been established in this age group (*see Sections 5.1 – Pharmacodynamic properties, Clinical trials and Sections 4.2 – Dose and method of administration*).

### Effects on laboratory tests

No data available

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Due to the presence of articaine**

***Interactions requiring precautions for use:***

**Other local anaesthetics*:***
Toxicity of local anaesthetics is additive. The total dose of all local anaesthetics administered should not exceed the maximum recommended dose of the drugs used.

**Cimetidine:**
Increased serum levels of amide anaesthetics have been reported after concomitant administration of cimetidine. Cimetidine may increase the cardiac and neurological effects of local anaesthetics.

**Sedatives (central nervous system depressants e.g. benzodiazepine, opioids):**
In children receiving benzodiazepines or opioids, reduced doses of SEPTANEST should be used due to additive effects.

**Due to the presence of adrenaline (epinephrine)**

***Interactions requiring precautions for use:***

**Halogenated volatile anaesthetics (e.g., halothane, enflurane):**
Reduced doses of SEPTANEST should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia.
Discussion with the anaesthetist before local anaesthetic administration during general anaesthesia is recommended.

**Postganglionic adrenergic blocking agents (e.g. guanethidine, and rauwolfia alkaloids):**
Reduced doses of SEPTANEST should be used under strict medical supervision followed by careful aspiration due to possible increase response to adrenergic vasoconstrictors, leading to the risk of hypertension and other cardiovascular effects.

**Non-selective beta-adrenergic blockers (e.g., propranolol):**
Reduced doses of SEPTANEST should be used due to possible increase in blood pressure and an increased risk of bradycardia.

**(TCAs) Tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, and protriptyline):**
If the concurrent use of these agents cannot be avoided, the dose and rate of administration of SEPTANEST should be reduced due to an increased risk of severe hypertension and dysrhythmia.

**MAO inhibitors [both A-selective (e.g. moclobemide) and non-selective (e.g. phenelzine, tranylcypromine, linezolide)]:**
If the concurrent use of these agents cannot be avoided, the dose and rate of administration of SEPTANEST should be reduced, and SEPTANEST should be used under strict medical supervision, due to possible potentiation of the effects of adrenaline leading to the risk of hypertensive crisis.

**COMT inhibitors (Catechol-O-methyl transferase inhibitors) (e.g. entacapone):**
Arrhythmias, increased heart rate and blood pressure variations may occur.
A reduced amount of adrenaline (epinephrine) in dental anaesthesia should be given to patients on COMT inhibitors.

**Drugs causing arrhythmias (e.g., antiarrhythmics like digitalis, quinidine):**
A reduced dose of SEPTANEST should be used due to the increased risk of arrhythmia when both adrenaline (epinephrine) and digital glucosides are administered concomitantly to patients.
Careful aspiration prior to administration is recommended.

**Thyroid hormones:**
When administered concomitantly with SEPTANEST, thyroid hormones can increase the adrenaline (epinephrine) concentration, leading to tachycardia, dysrhythmia, pulse alterations or myocardial ischemia.

**Ergot-type oxytocic drugs (e.g., methysergide, ergotamine):**
Use SEPTANEST under strict medical supervision due to additive or synergistic increases in blood pressure and/or ischemic response.

**Sympathomimetic vasopressors (e.g., mainly cocaine but also amphetamines, phenylephrine, pseudoephedrine, oxymetazoline):**
There is a risk of adrenergic toxicity.
If any sympathomimetic vasopressor has been used within 24 hours, the planned dental treatment should be postponed.

**Phenothiazines (and other neuroleptics):**
Use with caution in patients taking phenothiazines considering the risk of hypotension due to possible inhibition of adrenaline (epinephrine) effect.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

No effects on male or female fertility were observed in rats given articaine hydrochloride with adrenaline (epinephrine) subcutaneously from prior to mating until mating (males) or early gestation (females) at doses up to 80 mg/kg/day (approximately twice the maximum recommended human dose on a $mg/m^2$ basis).

### Use in pregnancy – Pregnancy Category B3

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

No clinical experience of the use of SEPTANEST in pregnant women is available.
Safe use of local anaesthetics during pregnancy has not been established with respect to adverse effects on fetal development. SEPTANEST should only be used in pregnancy when the benefits are considered to outweigh the risks.

No effects on embryofoetal development were observed when articaine hydrochloride with adrenaline (epinephrine) was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg/day in rabbits and 80 mg/kg/day in rats (approximately 2 times the maximum recommended human dose on a $mg/m^2$ basis).

In rabbits, foetal death and increased foetal skeletal variations were observed at the maternotoxic dose of 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/$m^2$ basis).

When articaine hydrochloride alone was administered subcutaneously to rats throughout gestation and lactation, 80 mg/kg/day (approximately 2 times the maximum recommended human dose on a mg/$m^2$ basis) increased the number of stillbirths, delayed eye opening, and adversely affected passive avoidance, a measure of learning, in pups, along with maternal toxicity were observed. A dose of 40 mg/kg/day (approximately the maximum recommended human dose on a mg/$m^2$ basis) did not produce these effects. A similar study using articaine hydrochloride with adrenaline (epinephrine) produced maternal toxicity, but no effects on the offspring.

**Use in lactation.**

It is unknown whether articaine or adrenaline (epinephrine) is excreted in human breast milk. The excretion of articaine or adrenaline (epinephrine) in milk has not been studied in animals. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with SEPTANEST should be made taking into account the benefit of breast-feeding to the child and the benefit of SEPTANEST therapy to the woman. Nursing mothers are advised to express and discard breast milk for approximately 4 hours after administration of articaine.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The combination articaine hydrochloride with adrenaline (epinephrine) acid tartrate solution for injection may have minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of the combination articaine hydrochloride with adrenaline (epinephrine) acid tartrate *(see section 4.8 - Adverse Effects).* Patients experiencing these symptoms should not drive or use machinery until any such symptoms have completely resolved.

## 4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Adverse reactions following administration of articaine / adrenaline (epinephrine) are similar to those observed with other local amide anaesthetics / vasoconstrictors. These adverse reactions are, in general, dose-related. They may also result from hypersensitivity, idiosyncrasy, diminished tolerance by the patient or unintentional intravascular injection. Nervous system disorders, local injection site reaction, hypersensitivity, cardiac disorders and vascular disorders are the most frequently occurring adverse reactions.

Serious adverse reactions are generally systemic. Early symptoms and signs of CNS toxicity include metallic taste, tinnitus, light-headedness and confusion, followed by tremors and shivering. Seizures and cardiorespiratory arrest may ultimately occur (*see Section 4.9 – Overdose*).

Tabulated list of adverse reactions

The reported adverse reactions come from spontaneous reporting, clinical studies and literature. The frequencies classification follows the convention: Very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). "Not known" indicates the frequency cannot be estimated from the available data.

Table 3 – List of Reported Adverse Reaction occurring after administration of articaine/adrenaline(epinephrine)

| **MedDRA System Organ Class** | **Frequency** | **Adverse Reactions** |
|---|---|---|
| Immune System disorders | Rare | Angioedema (face / tongue / lip / throat / larynx / periorbital oedema)<br><br>Bronchospasm/ asthma<br><br>Allergic[1], anaphylactic /anaphylactoid reactions<br>Urticaria |
| **Psychiatric disorders** | Rare | Nervousness/anxiety |
| | Not known | Euphoric mood |
| **Nervous System disorders** | Common | Neuropathy:<br>Neuralgia (neuropathic pain)<br>Hypoesthesia / numbness (oral and perioral)<br>Hyperesthesia<br>Dysesthesia (oral and perioral), *including*<br>Dysgeusia (e.g., taste metallic, taste disturbance)<br>Ageusia<br>Allodynia<br>Thermohyperesthesia<br>Presyncope, syncope<br>Headache<br>Restlessness, agitation<br>Confusional state, disorientation<br>Dizziness (light-headedness)<br>Tremor |
| | Uncommon | Burning sensation |
| | Rare | Deep CNS depression:<br>Loss of consciousness<br>Coma<br>Convulsion (including tonic- clonic seizure)<br>Facial nerve disorder[2] (palsy, paralysis and paresis)<br>Speech disorder (e.g. dysarthria, logorrhea) |

| | | |
|---|---|---|
| | | Vertigo<br>Balance disorder (disequilibrium)<br>Somnolence (Drowsiness)<br>Nystagmus |
| | Very rare | Paresthesia[3] (persistent hypoesthesia and gustatory loss) after mandibular or inferior alveolar nerve blocks |
| **Eye Disorders** | Rare | Horner's syndrome (eyelid ptosis, enophthalmos, miosis).<br>Diplopia (paralysis of oculomotor muscles)<br>Visual impairment (temporary blindness)<br>Ptosis<br>Miosis<br>Enophthalmos<br>Mydriasis<br>Blurred vision<br>Accommodation disorder |
| **Ear and labyrinth disorders** | Rare | Hyperacusis<br>Tinnitus |
| **Cardiac disorders** | Common | Bradycardia (also named bradyarrhythmia)<br>Tachycardia |
| | Rare | Palpitations<br>Cardiac arrest<br>Myocardial depression<br>Tachyarrhythmia (including ventricular extrasystoles and ventricular fibrillation)<br>Angina pectoris |
| | Not known | Conduction disorders (atrioventricular block, ventricular arrhythmias) |
| **Vascular disorders** | Common | Hypotension (with possible circulatory collapse)<br>Pallor |
| | Uncommon | Hypertension |
| | Rare | Hot flush |
| | Not Known | Vasodilatation<br>Vasoconstriction |
| **Respiratory, thoracic and mediastinal disorders** | Rare | Apnoea (respiratory arrest)<br>Dyspnoea[2]<br>Hypoxia<br>Hypercapnia<br>Bradypnoea<br>Tachypnoea<br>Yawning |
| | Not known | Dysphonia (Hoarseness)[1]<br>Respiratory depression |
| **Gastrointestinal disorders** | Common | Gingivitis<br>Swelling of tongue, lip, gums |

| | | |
|---|---|---|
| | Uncommon | Stomatitis, glossitis<br>Nausea, vomiting, diarrhoea |
| | Rare | Gingival / oral mucosal exfoliation (sloughing) / ulceration |
| | Not known | Dysphagia |
| **Skin and subcutaneous tissue disorders** | Uncommon | Rash (eruption)<br>Pruritus |
| | Not known | Erythema |
| **Musculoskeletal and connective tissue disorders** | Uncommon | Neck pain |
| | Rare | Muscle twitching<br>Chills (shivering) |
| | Not known | Aggravation of the neuromuscular manifestations in Kearns-Sayre syndrome |
| **General disorders and administration site conditions** | Uncommon | Injection site pain<br>Pain |
| | Rare | Injection site exfoliation / necrosis<br>Fatigue, asthenia (weakness) |
| | Not known | Local swelling<br>Post-operative swelling<br>Hyperhidrosis<br>Feeling hot<br>Feeling cold<br>Malaise |
| **Injury, poisoning and procedural complications** | Rare | Accidental injury |

Description of selected adverse reactions

[1] Allergic reactions should not be mistaken with syncopal episodes
[2] A 2-week delay in the onset of facial paralysis has been described following administration of articaine combined with adrenaline (epinephrine), and the condition was unchanged 6 months later.
[3] These neural pathologies may occur with various symptoms of abnormal sensations. Paraesthesia can be defined as spontaneous abnormal usually nonpainful sensation (e.g., burning, pricking, tingling or itching) well beyond the expected duration of anaesthesia. Most cases of paraesthesia reported following dental treatment are transient and resolve within days, weeks or months.
Persistent paraesthesia, mostly following nerve blocks in the mandible, is characterized by slow, incomplete, or lack of recovery. The risk of nerve damage is likely to be greater if repeated injections are given into a previously anaesthetized site or if higher concentration local anaesthetic solutions are administered.
Symptoms and signs of depressed cardiovascular function may result from a vasovagal reaction, particularly if the patient is in upright position.

Paediatric population

The safety profile was similar in children and adolescents from 4 to 18 years old compared to adults. However, accidental soft tissue injury was observed more frequently, especially in 3- to 7-year-old children, due to the prolonged soft tissue anaesthesia.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/

## 4.9 OVERDOSE

The most serious effects of articaine intoxication are on the CNS and cardiovascular system. The type of toxic reaction is unpredictable and depends on such factors as dosage, rate of absorption, unintended intravascular injection and clinical status of the patient. To minimise the risk, the patient's cardiovascular and respiratory vital signs and state of consciousness should be monitored after each injection.

Two types of reactions that effect stimulation and/or depression of the central cortex and medulla may result from systemic absorption.

- Slow onset symptoms following overdose include stimulation leading to restlessness, nervousness, dizziness, apprehension, light-headedness, paraesthesias, euphoria, logorrhoea, sweating, headache, blurred vision, tinnitus, nausea, vomiting, muscle twitching and tremors, nystagmus, tachypnoea, difficulty in swallowing, metallic taste, slurred speech and convulsions. Excitatory manifestations may not occur at all or may be transient, followed by depression with drowsiness, peripheral vasodilatation, hypotension, bradycardia, bradypnoea, cardiorespiratory arrest and coma.

- Rapid onset symptoms following overdose include depression, leading primarily to respiratory arrest, cardiovascular collapse, and cardiac arrest. Since cardiac arrest symptoms may occur rapidly and with little warning, treatment should be readily available.

**Treatment of overdose:**

*For all symptoms*

If acute toxicity occurs the injection should be stopped immediately. The patient should be placed in a recumbent position. Supportive treatment should be given; for circulatory depression this may require the administration of intravenous fluids and resuscitative drugs as directed by the clinical situation. A patent airway should be established and maintained, oxygen should be administered, and assisted or controlled ventilation should be provided as required.

*Circulatory collapse*

Immediately resuscitate with oxygen and commence cardiovascular resuscitation procedures as appropriate.

*Convulsions*

Appropriate medication for the management of convulsions should be used. Supportive treatment should be given; standard cardiopulmonary resuscitative therapy, including respiratory support may be required to counter adverse effects on the cardiovascular and/or respiratory systems and to control convulsions. There is no specific antidote.

If not treated immediately, both convulsions and cardiovascular depression may result in hypoxia, acidosis, bradycardia, arrhythmia and cardiac arrest.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Local anaesthetics/Articaine, ATC code: N01BB58

### Mechanism of action

Articaine is a local anaesthetic of the amide type. Preclinical pharmacodynamic studies show that the mechanism of action of articaine is similar to that of other commonly used anaesthetics (lidocaine, procaine, prilocaine). Inhibition of the generation and the conduction of the action potential but no change in resting potential is shown.

Articaine blocks sodium channels and, with lower sensitivity, potassium channels at neutral pH. Inhibition of muscle activation after nerve stimulation and depression of cardiac electrophysiologic measurements demonstrate that articaine has the same pharmacologic activities as other local anaesthetics. When injected close to sensitive nerve filaments, articaine has the reversible effect of blocking the conduction of painful sensations.

Adrenaline (epinephrine) added to the solution reduces bleeding during surgery, slows down the passage of articaine into the general circulation and thus ensures the prolonged maintenance of an active tissue concentration.

Adrenaline (epinephrine) acts on both adrenergic receptors of tissue innervated by sympathetic nerves, except for the sweat glands and arteries of the face. It is the most important alpha receptor activator. Adrenaline (epinephrine) stimulates the heart to increase output, raises the systolic blood pressure, lowers the diastolic blood pressure, relaxes bronchial spasm and mobilises liver glycogen, resulting in hyperglycaemia and possibly glycosuria.

The mean time to onset of anaesthesia after administration of articaine 4% with adrenaline (epinephrine) 1:100,000 is about 3.5 minutes with a range of 1 to 6 minutes, and the mean duration of anaesthesia is about 68 minutes with a range of 20 to 175 minutes. The pulpal analgesia lasts 75 minutes and the bleeding during surgery is significantly reduced.

### Clinical trials

Three randomized, double-blind, active-controlled studies were designed to evaluate effectiveness of SEPTANEST as a dental anaesthetic. A total of 882 patients received SEPTANEST 1:100,000. Of these, 7% were between 4 and 16 years old, 87% were between 17 and 65 years old, and 6% were at least 65 years old. In addition, 53% of patients were female and 47% were male, with a racial/ethnic distribution of 73% white, 11% Hispanic, 8% black, 5% Asian and 3% 'other' races/ethnicities. These patients underwent simple dental procedures, single apical resections and single crown procedures, and complex dental procedures such as multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures on the bone.

SEPTANEST 1:100,000 was administered as submucosal infiltration and/or nerve block. Efficacy was measured immediately following the procedure by having the patient and investigator rate the patient's procedural pain using a 10 cm visual analog scale (VAS), in which a score of zero represented no pain, and a score of 10 represented the worst pain imaginable. Mean patient and investigator VAS pain scores were 0.3 - 0.4 cm for simple procedures and 0.5 - 0.6 cm for complex procedures. These values are summarized in Table 4 below.

Table 4. Summary of VAS Pain Scores.

| | SEPTANEST 1:100,000 (articaine HCl 4% with adrenaline (epinephrine) acid tartrate 1:100,000) | |
|---|---|---|
| | Simple procedures | Complex procedures |
| Number of patients | 674 | 207 |
| Investigator score (cm)<br>Mean<br>Median<br>Range | <br>0.3<br>0.0<br>0 – 9.0 | <br>0.5<br>0.2<br>0 – 7.3 |
| Patient score (cm)<br>Mean<br>Median<br>Range | <br>0.4<br>0.0<br>0 – 8.0 | <br>0.6<br>0.2<br>0 – 8.7 |

In clinical trials, 61 paediatric patients between the ages of 4 and 16 years received SEPTANEST1:100,000. Among these paediatric patients, doses from 0.76 mg/kg to 5.65 mg/kg (0.9 to 5.1 mL) were administered safely to 51 patients for simple procedures and doses between 0.37 mg/kg and 7.48 mg/kg (0.7 to 3.9 mL) were administered safely to 10 patients for complex procedures. However, there was insufficient exposure to SEPTANEST 1:100,000 at doses greater than 7.00 mg/kg in order to assess its safety in paediatric patients. No unusual adverse events were noted in these patients. Approximately 13% of these paediatric patients required additional injections of anaesthetic for complete anaesthesia.

In the clinical trials 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received SEPTANEST 1:100,000. Among all patients between 65 and 75 years, doses from 0.43 mg/kg to 4.76 mg/kg (0.9 to 11.9 mL) were administered safely to 35 patients for simple procedures and doses from 1.05 mg/kg to 4.27 mg/kg (1.3 to 6.8 mL) were administered safely to 19 patients for complex procedures. Among the 11 patients ≥ 75 years old, doses from 0.78 mg/kg to 4.76 mg/kg (1.3 to 11.9 mL) were administered safely to 7 patients for simple procedures and doses of 1.12 mg/kg to 2.17 mg/kg (1.3 to 5.1 mL) were administered to 4 patients for complex procedures

*Clinical trial comparing SEPTANEST 1:100,000 and SEPTANEST 1:200,000*

A randomised, double-blind trial compared the difference in the surgeon's assessment of visualisation of the surgical field following the administration of up to 6.8 mL of SEPTANEST 1:100,000 versus SEPTANEST 1:200,000 during bilateral maxillary periodontal surgeries in 42 adult subjects aged between 22 and 65 years. SEPTANEST 1:100,000 was superior to SEPTANEST 1:200,000 in providing a clear visual field (83.3% versus 59.5%, p=0.0075) and less blood loss (54.9 mL versus 70.2 mL, p=0.175) during procedures. All patients achieved complete anaesthesia.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Following dental injection by the submucosal route of a 4% articaine solution containing 1:200,000 adrenaline (epinephrine), articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 minutes and 204 mg doses are 385 and 900 ng/mL, respectively.

### Distribution

Approximately 60 to 80 % of articaine hydrochloride is bound to human serum albumin and γ-globulins at 37°C in vitro.

### Metabolism

Articaine HCl is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid which is inactive. Articainic acid concentration reaches its peak about 30 to 60 minutes following the peak in articaine concentration. In vitro studies show that the human liver microsome P450 isoenzyme system metabolises approximately 5% to 10% of the available articaine with nearly quantitative conversion to articainic acid.

### Excretion

The elimination half-life of articaine is about 1.8 hours and that of articainic acid is about 1.5 hours. Articaine is excreted primarily through urine with 53 - 57% of the administered dose eliminated in the first 24 hours following submucosal administration. Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide, is also excreted in urine. Articaine constitutes only 2% of the total dose in excreted urine.

**Special Populations**
***Effect of Age*** **:** No pharmacokinetic data is available in the following populations: elderly, children.
***Race*** : No pharmacokinetic data is available for different racial groups.
***Renal and Hepatic Insufficiency*** : No pharmacokinetic data is available for patients with hepatic or renal impairment.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

Articaine was negative in bacterial and mammalian assays for gene mutation and a chromosomal aberration test in Chinese hamster ovary cells. *In vivo* clastogenicity (mouse micronucleous) assays with articaine alone and with adrenaline (epinephrine) were negative at a low subcutaneous dose (same as the maximal recommended clinical dose on a $mg/m^2$ basis).

### Carcinogenicity

Studies to evaluate the carcinogenic potential of articaine hydrochloride in animals have not been conducted.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

## 6.2 INCOMPATIBILITIES

In the absence of compatibility studies, SEPTANEST 1:100,000 and SEPTANEST 1:200,000 must not be mixed with other medicines.

## 6.3 SHELF LIFE

The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Protect from light.
Do not freeze.

## 6.5 NATURE AND CONTENTS OF CONTAINER

**SEPTANEST 1:100,000**
Box containing 5 blister trays of 10 x 1.7 mL (glass cartridge) with rubber closure.
Box containing 5 blister trays of 10 x 2.2 mL (glass cartridge) with rubber closure.

**SEPTANEST 1:200,000**
Box containing 5 blister trays of 10 x 1.7 mL (glass cartridge) with rubber closure.
Box containing 5 blister trays of 10 x 2.2 mL (glass cartridge) with rubber closure.

Not all pack sizes may be marketed

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

If only a portion of a cartridge is used, the remainder must be discarded. (*see section 4.2 DOSE AND METHOD OF ADMINISTRATION*)

# 7 MEDICINE SCHEDULE

Prescription Only Medicine

# 8 SPONSOR

IVOCLAR VIVADENT Ltd
12 Omega Street - Albany, Auckland - NEW ZEALAND
Telephone: 0508 486 252
Email: info.nz@ivoclarvivadent.com

# 9 DATE OF FIRST APPROVAL

**SEPTANEST 1:100, 000:** New Zealand Gazette 2/2/2006, No.10, p187

**SEPTANEST 1:200,000:** New Zealand Gazette 19/8/2021, 2021-go3523

# 10 DATE OF REVISION OF THE TEXT

01 June 2021

**SUMMARY TABLE OF CHANGES**

| Section changed | Summary of new information |
|---|---|
| All sections | Combined data sheet of Septanest 1:100,000 and 1:200,000 products |